

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
GAL EHRLICH
C/O ANTHONY CASTORINA
2001 JEFFERSON DAVIS HIGHWAY, SUITE 207
ARLINGTON, VA 22201

PCT

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Rule 71.1)

Date of mailing
(day/month/year) **12 APR 2007**

Applicant's or agent's file reference

27558

IMPORTANT NOTIFICATION

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/IL04/00181

24 February 2004 (24.02.2004)

27 April 2003 (27.04.2003)

Applicant

METABOGAL, LTD

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the *PCT Applicant's Guide*.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/ US

Mail Stop PCT, Attn: IPEA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
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Authorized officer

Manjunath N. Rao, Ph.D.

Telephone No. 571-272-1600

MANJUNATH N. RAO, PH.D.
PRIMARY EXAMINER

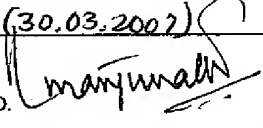
PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 27558	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/IL04/00181	International filing date (day/month/year) 24 February 2004 (24.02.2004)	Priority date (day/month/year) 27 April 2003 (27.04.2003)	
International Patent Classification (IPC) or national classification and IPC IPC: C12P 21/06; C12N 9/00, 9/14, 1/12, 1/20, 5/00, 15/00; C07H 21/04; A01H 11/00 USPC: 435/4, 6, 41, 69.1, 183, 195, 252.1, 252.3, 254.1, 320.1, 325, 410.; 536/23.1, 23.4, 23.5; 800/295			
Applicant METABOGAL, LTD			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of ___ sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. <input type="checkbox"/> (sent to the applicant and to the International Bureau) a total of ___ sheets, as follows: <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).			
4. This report contains indications relating to the following items: <div style="display: flex; flex-direction: column; gap: 5px;"> <div><input checked="" type="checkbox"/> Box No. I Basis of the report</div> <div><input type="checkbox"/> Box No. II Priority</div> <div><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</div> <div><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</div> <div><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</div> <div><input type="checkbox"/> Box No. VI Certain documents cited</div> <div><input type="checkbox"/> Box No. VII Certain defects in the international application</div> <div><input type="checkbox"/> Box No. VIII Certain observations on the international application</div> </div>			
Date of submission of the demand 29 November 2004 (29.11.2004)		Date of completion of this report 30 March 2007 (30.03.2007)	
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201		Authorized officer Manjunath N. Rao, Ph.D.  Telephone No. 571-272-1600	

Form PCT/IPEA/409 (cover sheet) (April 2005)

MANJUNATH N. RAO, PH.D.
PRIMARY EXAMINER

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. _____

PCT/IL04/00181 -

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

- ☒ the international application in the language in which it was filed.
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
- ☐ publication of the international application (under Rule 12.4(a))
- ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

- ☒ the international application as originally filed/furnished
- ☒ the description:
- pages 1-75 as originally filed/furnished
- pages* NONE received by this Authority on _____
- pages* NONE received by this Authority on _____
- ☒ the claims:
- pages 76-84 as originally filed/furnished
- pages* NONE as amended (together with any statement) under Article 19
- pages* NONE received by this Authority on _____
- pages* NONE received by this Authority on _____
- ☒ the drawings:
- pages 1-17 as originally filed/furnished
- pages* NONE received by this Authority on _____
- pages* NONE received by this Authority on _____
- ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International a

PCT/IL04/00181

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees the applicant has, within the applicable time limit:
- ☐ restricted the claims.
 - ☒ paid additional fees.
 - ☐ paid additional fees under protest, and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ neither restricted the claims nor paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:
- ☐ complied with.
 - ☒ not complied with for the following reasons:
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts
 - ☒ the parts relating to claims Nos. 1-24, 28-31, 33-37 and 42

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International
PCT/IL04/00181**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Claims <u>4, 12-24, 42</u>	YES
	Claims <u>1-3, 5-11, 28-31, 33-37</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-24, 28-31, 33-37, 42</u>	NO
Industrial Applicability (IA)	Claims <u>1-24, 28-31, 33-37, 42</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and Explanations (Rule 70.7)
Please See Continuation Sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International

PCT/IL04/00181

Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

a. type of material

☒

a sequence listing

☐

table(s) related to the sequence listing

b. format of material

☒

on paper

☒

in electronic form

c. time of filing/furnishing

☒

contained in the international application as filed

☒

filed together with the international application in electronic form

☐

furnished subsequently to this Authority for the purposes of search and/or examination

☐

received by this Authority as an amendment* on _____

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

V. 2. Citations and Explanations:

Claims 1-3, 5-11, 28-31, 33-37 lack novelty under PCT Article 33(2) as being anticipated by Martin et al. (DNA, 1988, Vol. 7, No.2, pages 99-106). Claims 1-3, 5-11, 28-31, 33-37 are drawn to a host cell producing a high mannose recombinant protein comprising a polynucleotide encoding the recombinant protein and a signal for causing the recombinant protein to be produced as a high mannose protein, wherein the polynucleotide comprises a first nucleic acid sequence encoding said protein of interest operably linked to a second nucleic acid sequence encoding a signal peptide wherein said signal peptide comprises a ER targeting peptide and wherein said host cell is a prokaryotic or a eukaryotic host cell and wherein said polypeptide is one of the lysosomal proteins such as glucocerebrosidase. Claim 28-31, 33-37 are also drawn to a recombinant biologically active high mannose lysosomal enzyme having at least one oligosaccharide chain comprising an exposed mannose residue. Martin et al. disclose one such host cell comprising a polynucleotide encoding said enzyme wherein said polypeptide is produced as a high-mannose protein in high levels. Martin et al. also disclose a recombinant glucocerebrosidase wherein said enzyme is inherently a biologically active high mannose lysosomal enzyme having at least one oligosaccharide chain comprising an exposed mannose residue. Thus, Martin et al. anticipate claims 1-3, 5-11, 28-31, 33-37 as written.

Claims 4, 12-24 and 42 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Boller et al. and Zhu et al. Claims 4, 12-24 and 42 are drawn to a host cell producing a high mannose recombinant protein comprising a polynucleotide encoding the recombinant protein and a signal for causing the recombinant protein to be produced as a high mannose protein, wherein the polynucleotide comprises a first nucleic acid sequence encoding said protein of interest operably linked to a second nucleic acid sequence with SEQ ID NO:1 encoding a signal peptide wherein said signal peptide comprises a ER targeting peptide and wherein said polynucleotide is operably linked to a third polynucleotide sequence with SEQ ID NO:2 encoding a plant vacuolar targeting sequence, and wherein said host cell is a plant cell and wherein said polypeptide

Supplemental Box

is one of the lysosomal proteins such as glucocerebrosidase. Claim 42 is drawn to a recombinant protein produced from a plant host cell. The reference of Martin et al. has already been discussed above. Martin et al. teach the production of glucocerebrosidase, a lysosomal protein recombinantly using a host cell comprising a polynucleotide with a signal sequence. The reference of Zhu et al. teach the polynucleotide encoding the signal peptide SEQ ID NO:1 and its use in producing novel recombinant proteins. On similar lines Boller et al. teach the vacuolar targeting sequence SEQ ID NO:2 and its use in targeting polypeptides into the vacuolar space. The invention as a whole is directed to production of glucocerebrosidase as a transgenic protein in plant host cells. The art and the above references teach and provide all sequences required for expressing the glucocerebrosidase as a transgenic protein. The production of mammalian proteins in plant products such as fruits and seed is well known since it eliminates the steps of purification and makes the recombinant protein ready for administration as a plant product. Therefore, with the above references in hand, it would have been obvious to one of ordinary skill in the art to produce human glucocerebrosidase, which is used in enzyme replacement therapy for lysosomal enzyme disorders, as a plant protein by expressing as a polynucleotide linked to the above signal sequence and vacuolar targeting sequences. One of ordinary skill in the art would have been motivated to do so since the lysosomal protein is extensively used in enzyme replacement therapy and production of the protein as a plant product would avoid the extensive purification steps and can be easily administered as a plant product. One of ordinary skill in the art would have had a reasonable expectation of success since Martin et al. already provide a host cell producing the high-mannose protein, Zhu et al. and Boller et al. provide the sequences to make a DNA construct to be expressed in a plant cell. Therefore the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

Claims 1-24, 28-31, 33-37, 42 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.